III. REMARKS

Applicants respectfully request entry of the above amendments and reconsideration of this application.

1. Status of the Claims

Claims 1-10 and 14-17 are pending in this application. Of these claims, Claims 14-17 have been withdrawn from consideration. Claims 11-13, 18 and 19 have been previously cancelled. Accordingly, Claims 1-10 are currently pending for examination on the merits.

2. Summary of the Amendments

As requested by the Examiner, the specification at page 16, line 23 has been amended to correct an obvious and inadvertent typographical error. Specifically, "2" in (-CH(NH_2)CH2-) has been corrected to be a "subscript 2 ", i.e., (-CH(NH_2)CH_2-). No new matter is introduced by this amendment.

The specification has also been amended to replace the term "HPLC" with "high-performance liquid chromatography (HPLC)" as requested by the Examiner. Since the term "HPLC" is well-known to those skilled in the art to mean "high-performance liquid chromatography," no new matter is introduced by this amendment.

Claim 1 has been amended to individually set forth each of the components of the pharmaceutical composition using subparagraph headings (i.e., "(a)" and "(b)"). Additionally, the semicolon following "antibiotic" has been deleted. As discussed more fully below, these formatting changes are being made to address the Examiner's concern that it is unclear which component the phrase "or a pharmaceutically acceptable salt thereof" refers to. Claims 5 and 6 have been amended in a similar manner. Support for these amendments is found throughout the specification, for example, on page 2, at line 28; page 7, at line 12; page 12, at line 06; page 31, at lines 14-19; and page 39, at lines 10-11; and in Claims 6, 12 and 13 as originally filed.

These amendments are being made for essentially cosmetic reasons and not for any

reason substantially related to a requirement for patentability. Entry of these amendments is respectfully requested.

3. Requirement for Restriction Under 35 U.S.C. §121

The Examiner has indicated that restriction to one of the following inventions is required under 35 U.S.C. §121:

Group I: Claims 1-10 drawn to a pharmaceutical composition comprising a cyclodextrin and a lipidated glycopeptide antibiotic, classified in Class 514, Subclasses 8, 58 and 183, and Class 530, Subclass 395; and

Group II: Claims 14-17 drawn to a method of treating a disease state in a mammal comprising administering to the mammal the pharmaceutical composition thereof and a method of reducing tissue accumulation in a mammal of a lipidated glycopeptide antibiotic, classified in Class 514, Subclasses 8 and 53.

In a telephone conversation with the Examiner on August 25, 2003, Applicants provisionally elected Group I, i.e., Claims 1-10, with traverse. Applicants affirm the election of Group I, but traverse this requirement for restriction for the following reasons.

The Examiner is required to conduct a search and examination of the entire application even though it includes claims to independent or distinct inventions if the search and examination can be made without serious burden. See MPEP §803. In the present case, the Examiner has not indicated in any way why a search of the entire application would create a serious burden. In fact, any search for the pharmaceutical compositions of this invention would by necessity also produce prior art relating to the use of such compositions. This is evidenced by the fact that the claims of Group II are classified in the same class and subclasses (i.e., Class 514, Subclasses 8 and 53) as those in Group I. Thus, the Examiner would not be required to search any additional classes or subclasses in order to search Group II along with Group I. Accordingly, a search and examination of the entire application can be made without serious burden and

therefore, the Examiner is required to conduct such a search and examination of the entire application. Accordingly, Applicant respectfully requests that the Examiner withdraw the restriction for requirement imposed on the pending claims under 35 U.S.C. §121.

Should the Examiner choose to maintain this restriction requirement, Applicants respectfully requested rejoinder of any product claims that are found to be allowable with any method of use claims which depend from or otherwise include all the limitations of the allowed product claims as provided for in MPEP §821.04 and *In re Ochiai* 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995).

4. Objections to the Specification and Claims

The Examiner has objected to the specification because of several informalities. Specifically, the Examiner has indicated that on page 16, line 23, "(-CH(NH_2)CH2-)" should be changed to "(-CH(NH_2)CH_2-)"; and on page 36, line 4, "HPLC" should be written in full at the first instance of its use. In response, Applicants have amended the specification as suggested by the Examiner. Accordingly, these objections may be withdrawn.

Additionally, the Examiner has indicated that in Claim 6, a verb is missing after "provided that...." In response, Applicants note that the entire phrase used in Claim 6 is as follows: "provided that the components of the composition total 100 weight percent." In this phrase, the word "total" functions as the verb in accordance with its commonly-accepted dictionary meaning. Accordingly, since this phrase contains a verb, this objection may be withdrawn.

5. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-10 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Specifically, the Examiner has indicated that Claim 1 recites "or a pharmaceutically acceptable salt thereof" and that it is allegedly unclear to which

component this phrase is referring to.

While not agreeing with the Examiner's conclusion, Applicants have amended Claims 1, 5 and 6 to clarify that the phrase "or a pharmaceutically acceptable salt thereof" refers to the lipidated glycopeptide component. Specifically, each of the components of the pharmaceutical composition is now set out in separate subparagraphs so there can be no uncertainty as to which component the phrase "or pharmaceutically acceptable salts thereof" refers to. In view of these amendments, Applicants respectfully request that this reject be withdrawn.

6. Rejections Under 35 U.S.C. §102

Claims 1, 2, 5, 7 and 8 have been rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,776,912, issued to Patel et al. Additionally, Claims 1-10 have been rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,624,914, issued to Patel et al. For the following reasons, these rejections are respectfully traversed.

Anticipation under 35 U.S.C. §102(b) requires that each and every element of the claimed invention be disclosed in a prior art reference. A prior art reference that merely discloses similar but not identical elements is insufficient to anticipate the claimed invention.

In the present case, Applicants are claiming pharmaceutical compositions comprising (a) a cyclodextrin and (b) a lipidated glycopeptide antibiotic or a pharmaceutically acceptable salt thereof. The term "glycopeptide antibiotic" is a term of art used by those skilled in the art to refer to a specific class of antibiotics having a heptapeptide backbone. For example, the Examiner's attention is respectfully directed to the review article by K.C. Nicolaou et al. entitled "Chemistry, Biology, and Medicine of the Glycopeptide Antibiotics", *Angew. Chem. Int. Ed.*, 1999, *38*, 2097-2152, which was provided in the Information Disclosure Statement filed on November 8, 2001. This review article, which was published shortly before the priority documents for the present application, is a representative example of a much larger body of art which establishes that the term "glycopeptide antibiotic" refers of a specific class of antibiotics.

Moreover, the term "lipidated glycopeptide antibiotic" refers to a glycopeptide antibiotic

which has been synthetically modified to a contain a lipid substituent. In this regard, the Examiner's attention is respectfully directed to the present specification at page 29, lines 14-24, and the references cited therein.

Turning now to the cited references, U.S. Patent Nos. 5,624,914 and 5,776,912 disclose pharmaceutical compositions containing a cyclodextrin and a lipophilic oligosaccharide antibiotic. The antibiotics disclosed in these documents are members of the orthosomycin family of antibiotics not the glycopeptide family of antibiotics (see, for example, Column 1, lines 14-19 of the '912 patent, and Column 1, lines 19-25 of the '914 patent). These two families of antibiotics are structurally distinct and dissimilar as can be seen by the formulas shown in the '912 and '914 patents.

Accordingly, since the cited references do not disclose each and every element of the presently claimed invention, i.e., the lipidated glycopeptide antibiotic, these references cannot anticipate the subject matter of the present claims under 35 U.S.C. §102(b). Therefore, Applicants respectfully request that these rejections be withdrawn.

7. Rejections Under 35 U.S.C. §103

Claims 1, 2, 5, 7 and 8 have been rejected under 35 U.S.C. §103(a) as being unpatentable over EP 463 653 A1, to Roberto et al., in view of U.S. Patent No. 4,639,433, to Hunt et al. Additionally, Claims 3, 4, 6, 9 and 10 have been rejected under 35 U.S.C. 103(a) as being unpatentable over EP 463 653 A1, to Roberto et al., in view of U.S. Patent No. 4,639,433, to Hunt et al., and in further view of EP 094 157 A1, to Hirai et al., U.S. Patent No. 6,048,845, to Rubinfeld, and Pea et al., *Journal of Antimicrobial Chemotherapy* (2000) **45**, 329-335. For the following reasons, these rejections are respectfully traversed.

The presently claimed subject matter is directed to a pharmaceutical composition comprising (a) a cyclodextrin and (b) a lipidated glycopeptide antibiotic or a pharmaceutically acceptable salt thereof; and to methods of using such pharmaceutical compositions. Surprisingly, Applicants have discovered that combining a cyclodextrin with a lipidated glycopeptide

antibiotic reduces or eliminates several undesired properties of the lipidated glycopeptide antibiotic, including reducing nephrotoxicity and excessive tissue accumulation of the lipidated glycopeptide antibiotic (see, for example, page 1, lines 19 to 23 of Applicants specification).

The Examiner has taken the position that the cited references provide one skilled in the art with the motivation to combine a cyclodextrin with a lipidated glycopeptide antibiotic. Specifically, the Examiner has indicated that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made would [sic] have combined the teachings of the above references because Robert [sic] et al. teach a pharmaceutical composition comprising a cyclodextrin and peptide antibiotic, Hunt et al. teach the type of the peptide antibiotic is a lipidated glyco-peptide antibiotic, and Hirai et al. teach a pharmaceutical composition comprising cyclodextrin and the bioactive component, e.g., peptide antibiotic, the weight percent of the cyclodextrin and freeze-dried power [sic] form of the composition. When combined, there would be the following advantages: (i) high level of bioavailability (see page 15, line 25), (ii) improve drug efficacy in view of biological half-life of the administrated drug (see page 18, lines 30-34), (iii) low cyctotoxicity (see page 18, lines 34-38) and (iv) permutable repeated dose regimens (see page 18, lines 21-38), as taught by Hirai et al. Cyclodextrin-formulated pharmaceutical compositions has an especial [sic] benefit for formulating cyctotoxic drug, e.g., antibiotic such as glycopeptide antibiotic, i.e., bleomycins (see abstract and column 11, lines 48-53 of the Rubinfeld et al. patent), and, it has been known in the prior art of record that use of cyclodextrin in the pharmaceutical composition reduces the cytotoxicity of the composition (see the Roberto et al. teaching , especially abstract), which would be, therefore, noticeably advantageous to the glyco-peptide antibiotics which have undesirable nephrotoxicity, e.g. vancomycin (see the Pea et al. reference, at page 330, the left column, lines 3-4).
>
> Given the above motivation, one of ordinary skill in the art would have combined the teaching of the above references to develop the pharmaceutical composition comprising the potential toxic glyco-peptide antibiotic and the cyclodextrin for achieving high pharmaceutical efficacy and lower cytotoxicity of the antibiotics. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made. (Office Action beginning at page 8, third paragraph).

Assuming for the sake of argument that the cited references provide sufficient motivation to establish a *prima facie* case of obviousness, it is well established that a *prima facie* case of obviousness can be rebutted by evidence showing that the claimed subject matter possesses a superior or unexpected property.

In the present case, Applicants have presented data in the specification demonstrating that the claimed composition provides both reduced tissue accumulation and reduced nephrotoxicity. Specifically, Applicants demonstrate in Example 6 (beginning on page 53, line 20) that a cyclodextrin dramatically reduces tissue accumulation (Table 1 on page 54) and nephrotoxicity (Table 2 on page 55) for a lipidated glycopeptide antibiotic. For the Examiner's convenience, Tables 1 and 2 are reproduced herein as follows:

TABLE 1

Tissue Distribution and Urinary Recovery for Compound A in Various Formulations Following Intravenous Infusion to Female Rats at a dose of 50 mg/kg. (Values are Mean (SD))

Compound (Formulation)	Serum Conc. (μg/mL)	% Recovered (as unchanged parent)		
		Urine	Liver	Kidney
Compound A (25% CD)	0.86 (0.19)	90.91 (8.39)	1.90 (0.32)	0.62 (0.12)
Compound A (5% CD)	1.66 (0.33)	40.51 (18.57)	4.89 (0.81)	2.08 (0.43)
Compound A (1% CD)	17.1 (12.1)	17.45 (6.92)	8.47 (0.46)	5.68 (2.49)
Compound A (D5W)	59.8 (27.1)	12.61 (4.60)	14.19 (3.41)	17.82 (4.94)

CD = hydroxypropyl-β-cyclodextrin

D5W = aqueous 5% dextrose solution

As shown in Table 1, urinary recovery of Compound A was significantly higher in formulations contain a cyclodextrin; and liver and kidney accumulation were significantly lower in such formulations. For example, urinary recovery of the lipidated glycopeptide antibiotic went from 12.61% without cyclodextrin to 90.91% with a 25 weight percent cyclcodextrin formulation. Similarly, liver accumulation went from 14.19% without cyclodextrin to 1.90% with a 25 weight percent cyclodextrin formulation.

TABLE 2

Effects of Compound A Formulation on Serum Renal Chemistry

Compound	Formulation	BUN (mg/dL)	Creatinine (mg/dL)
Vehicle	25% (w/v) CD	14 ± 1	0.26 ± 0.06
Compound A	25% (w/v) CD	13 ± 2	0.26 ± 0.02
Vehicle	5% (w/v) CD	10 ± 1	0.21 ± 0.01
Compound A	5% (w/v) CD	18 ± 5	0.31 ± 0.07
Vehicle	1% (w/v) CD	13 ± 2	0.24 ± 0.01
Compound A	1% (w/v) CD	26 ± 5	0.34 ± 0.08
Vehicle	D5W	12 ± 2	0.28 ± 0.02
Compound A	D5W	67 ± 2	0.72 ± 0.08

CD = hydroxypropyl-β-cyclodextrin

D5W = aqueous 5% dextrose solution

The results in Table 2 show that the formulations containing cyclodextrin had significantly less nephrotoxicity compared to formulations without cyclodextrin. For example, BUN levels decreased from 67 ± 2 mg/mL to 13 ± 2 mg/mL (equivalent to vehicle alone) when the lipidated glycopeptide was formulated with 25 weight percent glycopeptide.

Accordingly, the data in Tables 1 and 2 clearly demonstrate that cyclodextrins have surprising and unexpected effects on the tissue accumulation and nephrotoxicity of lipidated glycopeptide antibiotics.

In contrast, the cited references do not teach or suggest that pharmaceutical compositions comprising a cyclodextrin and a lipidated glycopeptide antibiotic would have either reduced tissue accumulation or reduced nephrotoxicity compared to formulations without the cyclodextrin. First, none of the cited references even discuss the problem of tissue accumulation of lipidated glycopeptide antibiotics – let alone suggest a solution to this problem. Accordingly, in view of the teachings of the cited references, Applicants presently claimed pharmaceutical compositions provide a surprising and unexpected result, i.e., reduced tissue accumulation of a lipidated glycopeptide antibiotic. This surprising and unexpected result, which is neither taught nor suggested by the cited references, is sufficient on its own to rebut a *prima facie* case of obviousness. Therefore, based on these data alone, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

In addition, however, the cited references do not teach or suggest that pharmaceutical compositions comprising a cyclodextrin and a lipidated glycopeptide antibiotic would have reduced nephrotoxicity compared to formulations without the cyclodextrin.

For example, the Rubinfeld reference discloses that "extravasation-associated ulceration" and related irritation caused by cytotoxic compounds can prevented by using a cyclodextrin (see, for example, column 5, lines 18-42). Thus, the Rubinfeld reference is not concerned with nor does it suggest a solution to the problem of nephrotoxicity caused by lipidated glycopeptide antibiotics.

The Hirai et al. reference is directed to pharmaceutical compositions containing a hydrophilic drug and a cyclodextrin, and the administration of such pharmaceutical compositions through, for example, the nasal cavity (see, for example, page 2, lines 01-08). In this regard, Harai et al. teach that cyclodextrin itself has low toxicity (page 18, lines 34-38). However, as with the Rubinfeld reference, the Harai et al. reference is not concerned with nor does it suggest a

solution to the problem of nephrotoxicity caused by lipidated glycopeptide antibiotics.

Additionally, the Hunt et al. reference merely teaches a particular type of lipidated glycopeptide antibiotic but does not teach or suggest the problem of nephrotoxicity of such compounds or a solution to the problem. Similarly, the Pea et al. reference identifies the problem of nephrotoxicity caused by a glycopeptide antibiotic (i.e., vancomycin) but suggests only the solution of measuring serum concentrations of vancomycin to avoid nephrotoxicity (see page 330, left column, lines 1-5).

Finally, the Roberto et al. reference discloses pharmaceutical compositions comprising a drug, an enhancer of absorption at a mucosal surface and a cyclodextrin (see, for example, column 3, lines 16-23). This reference teaches that when an absorption enhancer is used in combination with a cyclodextrin, the undesirable side effects due to the enchancer (such as lipid disruption) may be reduced (see column 3, lines 09-15).

The Roberto et al. reference does not disclose lipidated glycopeptide antibiotics nor does it disclose the problem of nephrotoxicity caused by lipidated glycopeptide antibiotics. Accordingly, Applicants' discovery of the dramatic reduction in nephrotoxicity is certainly surprising and unexpected in view of this reference.

Moreover, the Roberto et al. reference actually reports that rat nasal tissue exposed to 2-hydroxypropyl-β-cyclodextrin showed some signs of interaction between the epithelium and the dose (see column 17, lines 05-12). More specifically, Roberto et al. report:

> On close inspection, the epithelium on the dosed side appeared to be more "disordered" than the control tissue with the line of cilial basal bodies at the luminal surface interrupted at intervals. The nuclei of the epithelial cells on the dosed side tended to be smaller and more irregularly shaped than the large rounded nuclei in the untreated epithelium, particularly over the central septum areas. Also dosed nuclei were stained more densely obscuring intranuclear detail and tended to be more closely packed at the basal membrane. These observations suggest some interaction between dose and tissue, possibly in the early stages. Column 17, lines 22-35.

Accordingly, Applicants' discovery of reduced nephrotoxicity is even more unexpected and surprising in view of this teaching by Roberto et al. that cyclodextrins effect epithelial cells.

Thus, in summary, none of the cited references either alone or when combined with each other teach or suggest that pharmaceutical compositions comprising a cyclodextrin and a lipidated glycopeptide antibiotic would have reduced tissue accumulation and reduced nephrotoxicity compared to formulations without the cyclodextrin. Accordingly, Applicants' data are surprising and unexpected in view of the cited references and as a result, such data are sufficient to rebut a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

8. Obviousness-Type Double Patenting Provisional Rejection

Claims 1, 2, 5 and 17 have been provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over Claims 10 and 17 of co-pending U.S. Application Serial No. 09/674,266.

In response, Applicants submit herewith a Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c). The requisite fee under 37 C.F.R. §1.20(d) is also enclosed herewith. Accordingly, this provisional rejection may be withdrawn.

9. Request for a Telephone Interview

Applicants respectfully request a telephone interview with the Examiner and the Supervisory Examiner having signatory authority for this application to discuss the pending rejections and this response. The Examiner is respectfully requested to telephone the undersigned attorney at (650) 808-6406 to schedule a mutually convenient time for the interview. A PTO Form PTOL-413A is submitted herewith.

Consideration of the above amendments and remarks is respectfully requested. Applicants believe this application is now is condition for allowance and a notice to that effect is respectfully requested. Should there be any questions concerning this response, the Examiner is requested to telephone the undersigned attorney at (650) 808-6406.

Respectfully submitted,

THERAVANCE, INC.

Date: December 10, 2003

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